25. The nucleic acid of Claim 24 wherein the derivative is a derivative of a glycoprotein of a herpes simplex virus type 1 or type 2, and the pathogen is herpes simplex type 1 and/or type 2.

26. An expression vector comprising a nucleic acid according to Claim 24.

27. A stable host cell comprising an expression vector according to Claim 26.

28. A host cell according to Claim 27 wherein the host cell is a eukaryotic cell.

29. A host cell according to Claim 28 wherein the host cell is a mammalian host cell.

30. A method of producing a truncated, membrane-free derivative of a polypeptide comprising a membrane-binding domain and antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by a pathogen, said method comprising:

(a) culturing the host cell of Claim 27; and

(b) recovering the derivative from the culture.

These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with the Examiner's position. In accordance with the requirements of 37 C.F.R. §1.121, a marked up version showing the changes to the claims, is attached herewith as Appendix A.

REMARKS

It is Applicants' understanding that the Examiner to whom the present application was previously assigned has left the Patent Office. In the interest of expediting the prosecution of this application, Applicants respectfully request an Examiner Interview after the new Examiner has reviewed this Amendment. The Examiner is requested to telephone the undersigned at (510) 337-7871 to schedule an interview.

Status of the Claims.

Claims 1-8 and 10-30 are pending with entry of this amendment, Claim 9 being canceled and Claims 16-30 being added. Claims 1-8 and 10-15 are amended. Support for the amendments to Claims 1-15 is found in the specification at least at page 34, lines 4-23. Additional support for the amendment to Claim 4 is found at least at page 2, lines 20-22. Support for Claims 18, 19, and 20 is found at least in Claims 11, 12, and 15, respectively. Claims 21 and 22 find

support in the specification at least a page 2, lines 20-22. Claims 23-25 find support in the specification at page 24, line 10 through page 25, line 9. This passage also supports Claims 26-29, when taken with Claims 11 and 12. Claim 30 finds support generally throughout the specification (see, e.g., page 25, lines 11-17). Accordingly, these amendments introduce no new matter.

Under 37 C.F.R. § 1.116, amendments to the claims after final rejection may be entered if the amendments place the claims in better form for consideration on appeal. Applicants submit that the above amendments meet this criterion. These amendments are necessary to more clearly recite Applicants' invention. The amendments were not presented earlier because the need for the amendments was not apparent until the Final Office Action was received. Entry of the amendments is thus permitted under § 1.116 and is respectfully requested.

Applicants appreciate the Examiner's allowance of Claims 2, 6-8, 14, and 15. Applicants believe that the above amendments do not affect the allowability of these claims. The allowed claims were amended to ensure proper antecedent basis and consistent use of terminology throughout the claims, and the amendments are thus merely editorial in nature.

The Invention

The invention includes methods and compositions relating to a truncated, membrane-free derivative of a normally membrane-bound polypeptide, which is characterized by a membrane-binding domain and antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by a pathogen. As recited in Claim 1, the derivative "is devoid of the membrane-binding domain," but still "has exposed antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by the pathogen." As stated in the specification:

> The success of this invention in demonstrating that a truncated form of a membrane bound protein, lacking that part of the hydrophobic-hydrophilic carboxy-terminal region responsible for binding it to the membrane, can yet be immunogenic indicates that similar results can be expected with other immunogenic membrane bound proteins, thus providing an improved source of vaccine against viruses, parasites and other pathogenic organisms.

Applicants' specification, at page 34, lines 4-10. As those of skill in the art would have readily appreciated, truncated forms of pathogen proteins that can be conveniently produced and yet are capable of eliciting antibodies have other applications, such as for use as an immunogen to produce

antibodies for diagnostic assays. Those of skill in the art would also have appreciated that such truncated proteins could also be employed as standards in such diagnostic assays.

Importantly, the invention relates to "a truncated, membrane-free derivative of a polypeptide comprising a membrane-binding domain and antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by a pathogen," as recited in Claim 1. Applicants discovered that, surprisingly, the deletion of the membrane-binding domain did not abolish the ability of the derivative to elicit antibodies that bind to the native protein. Even more surprising, as demonstrated with the herpes glycoprotein gD, these antibodies were shown to neutralize infectivity of the pathogen. Claim 1 relates to an immunogenic composition comprising such a truncated, membrane-free derivative. Claim 10 relates to a method of producing such an immunogenic composition and incorporates all of the elements of Claim 1 by reference to the immunogenic composition recited in Claim 1. Claim 23 relates to a nucleic acid encoding a truncated, membrane-free derivative identical to that recited in Claim 1, and Claims 26 and 27 relate, respectively, to a vector comprising this nucleic acid and a host cell comprising the vector. Claim 30 relates to a method of producing an immunogenic composition that entails "culturing the host cell of Claim 27; and . . . recovering the derivative from the culture." All of the other pending claims depend from one of these claims. Thus, all of the pending claims either recite or incorporate by reference the important feature of the invention described above, namely:

> An immunogenic composition comprising a truncated, membrane-free derivative of a polypeptide comprising a membrane-binding domain and antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by a pathogen, ***wherein said derivative:***
>
> ***(a) is devoid of the membrane-binding domain*** whereby the derivative is free of membrane, ***and***
>
> ***(b) has exposed antigenic determinants capable of raising neutralizing antibodies against in vivo challenge by the pathogen*** . . .
>
> .

See Claim 1 (emphasis added). Accordingly, it is believed that the pending claims are commensurate with Applicants' contribution to the art.

Applicants also established that the truncated derivative of a pathogen protein could be expressed in a stable eukaryotic cell line, such as, a mammalian cell line, and recovered from the cell culture medium. This secreted derivative of the pathogen protein unexpectedly retained the

capability of eliciting antibodies that bind to the native protein and neutralize infectivity of the pathogen. These features of the invention are recited in Claims 11 and 12, relating to production methods; Claims 18 and 19, relating to immunogenic compositions; and Claims 27-29, relating to vectors.

35 U.S.C. §112, First Paragraph.

Claims 1, 3-5 and 9-13 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. Office Action, at 2. The rejection is respectfully traversed.

In support of the rejection, the Examiner stated:

> The claims are broadly drawn to a vaccine and a method of making a vaccine against any pathogen or to a method of immunizing a patient against herpes by administering a truncated membrane free derivative of a membrane bound polypeptide.

Office Action, at 2. This statement does not apply to the amended claims, which relate to an immunogenic composition. Furthermore, none of the previously pending claims, nor any of the amended claims, recites a method of immunizing a patient against herpes.

The Examiner also alleged that "the specification does not contain sufficient guidance or teaching to enable a vaccine against herpes by administering a truncated, membrane free derivative of a membrane bound polypeptide other than glycoprotein D. Although Applicants disagree with the Examiner for the reasons expressed repeatedly throughout the long prosecution of this application, the point is now moot, as the claims recite an immunogenic composition and a related nucleic acid, vector, and host cell, and production methods. Thus, the Examiners' statement that "the role of the gC, gF or other glycoproteins ingenerating protective immune responses has not been clearly defined" is irrelevant to the claimed invention, as are the Examiner's comments relating to alleged difficulties with using a mouse model to identify proteins or peptides that are presumed to be improtant for inducing immunity to HSV. Office Action, at 3.

At page 3 of the Office Action, the Examiner suggested that the previously presented arguments were not congruent with the claims, stating that "the claims are not drawn to immunogenic compositions, but recite vaccines." This purported defect has been overcome by amending the claims to relate to immunogenic compositions and related compositions and methods.

The Examiner apparently viewed the Rose Declaration, filed by Applicants, as corroborating his views regarding the unpredictability of producing successful vaccines of the type

previously claimed. Specifically, the Examiner found support for his position in Dr. Rose's statement that "one of ordinary skill in the art could not have predicted that a successful vaccine that raises neutralizing antibodies could have been produced based essentially on a truncated, membrane free derivative of a membrane-bound glycoprotein of the virus." Office Action, at 4. This view misses the point. Dr. Rose's statement relates to the expectation in the art prior to Applicants' invention. In any event, the Examiner's point is moot in light of the amendments to the claims.

In concluding his discussion of the §112, first paragraph rejection, the Examiner summarized as follows:

> [I]t appears that one of skill in the art would not have expected the data which appears to show protection from herpes 1 or 2 employing glycoprotein D to correlate to protection from other pathogens, including herpes virus, employing other glycoproteins. Nor would one of skill in the art expect *in vitro*, mouse, and/or rabbit data to correlate to humans. The Secher declaration states that an animal needs to be protected from disease in order to support the terminology "vaccine". There is nothing of record which shows that any other glycoproteins were protective or that animals were protected from any disease other than Herpes 1 or 2.

This rationale does not support a rejection of the amended claims. Accordingly, withdrawal of the rejection is respectfully requested.

Conclusion.

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

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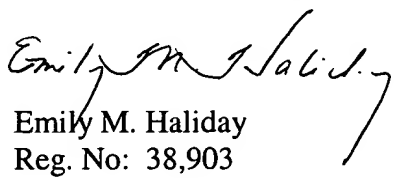
Respectfully submitted,



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